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(71) Applicant
Merck & Co Inc

(Incorporated in the USA – New Jersey)

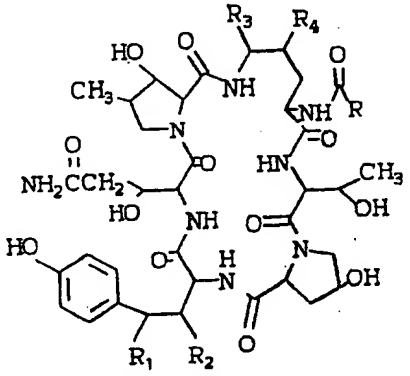
P O Box 2000, Rahway, New Jersey 07065, United States of America

(72) Inventor
Milton L Hammond

(74) Agent and/or Address for Service
J Thompson
Merck & Co., Inc
European Patent Department, Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR, United Kingdom

(54) N-acylated cyclohexapeptide compounds

(57) Compounds of the formula



(I)

wherein R is C_{6-23} alkyl or alkenyl, aryl or heteroaryl and wherein (1) R_2 is hydrogen and R_1, R_3 and R_4 are hydroxy, (2) R_1, R_2 and R_4 are hydrogen and R_3 is hydroxy; or (3) R_1, R_2, R_3 and R_4 are hydrogen.

The compounds have antifungal properties and may be used to combat *pneumocystis carinii* infection.

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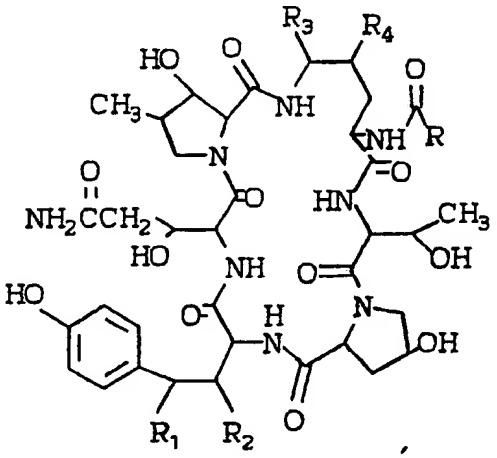
TITLE OF THE INVENTION

N-ACYLATED CYCLOHEXAPEPTIDE COMPOUNDS

The present invention is directed to novel semi-synthetic compounds having the formula



(I)

In this and succeeding formulas, R is

a) a straight or branched chain alkyl from 5 to 23 carbon atoms;

b) a straight or branched chain alkenyl from 5 to 23 carbon atoms;

c) aryl, preferably phenyl and substituted phenyl wherein the substituent is selected from C_1 to C_{10} alkyl, C_1 to C_{10} alkoxy or C_1 to C_{10} thioalkoxy; or

d) heteroaryl, preferably pyrryl, thiophenyl, furyl, indolyl, benzothiophenyl, benzofuryl, imidazolyl, benzimidazolyl or pyridinyl, and

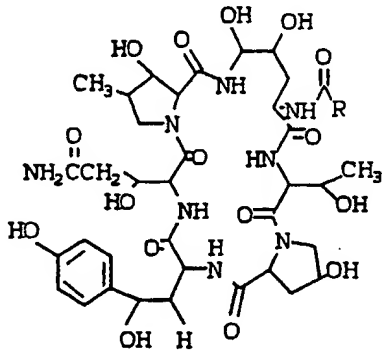
R_1, R_2, R_3 and R_4 may be hydrogen or hydroxy to provide a preferred nucleus selected from those in which

(1) R_2 is hydrogen and R_1, R_3 and R_4 are hydroxy,

(2) R_1, R_2 and R_4 are hydrogen and R_3 is hydroxy; and

(3) R_1, R_2, R_3 and R_4 are hydrogen.

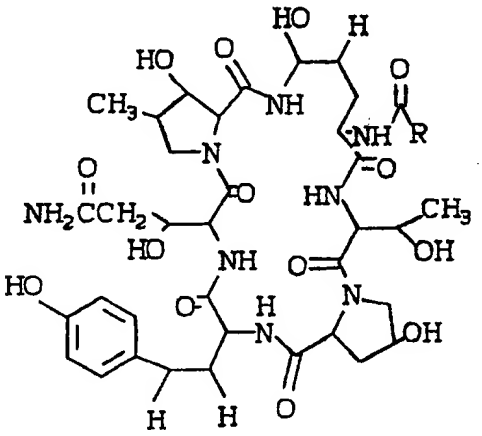
When R_2 is hydrogen and R_1, R_3 and R_4 are hydroxy, the compound may be represented by the formula (Ia)



(Ia)

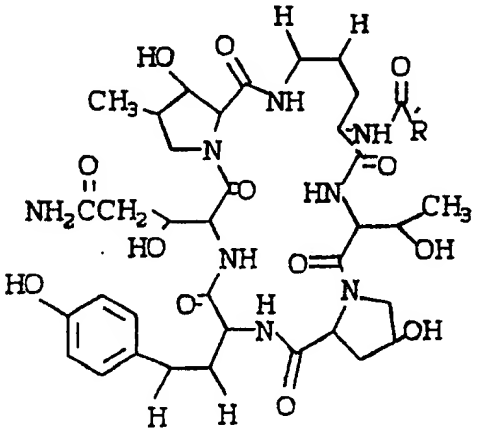
Representative R groups when R is alkyl are octadecyl, hexadecyl, dodecyl, decyl, tetradecyl, tridecyl, pentadecyl and the like.

When R_1, R_2 and R_4 are hydrogen and R_3 is hydroxy, the compound may be represented by the formula (Ib)



(Ib)

When R_1, R_2, R_3 and R_4 are hydrogen, the compound may be represented by the formula (Ic)



(Ic)

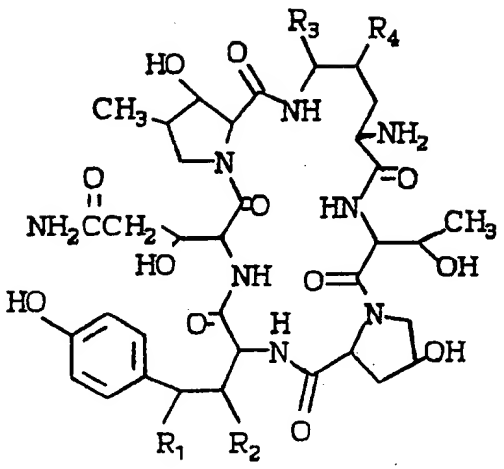
Representative R groups when R is alkyl are octadecyl, hexadecyl, dodecyl, decyl, tetradecyl, tridecyl, pentadecyl and the like.

Representative R groups when R is alkenyl are 8,11-heptadecadienyl, 2-hexenyl, 4-octenyl, 7-pentadecenyl, 8-heptadecenyl, 10-heptadecenyl and the like.

Representative R groups when R is aryl and substituted aryl are phenyl, tolyl, xylyl, 2-ethylphenyl, 4-ethylphenyl, 4-isopropylphenyl, 4-isooctylphenyl, 4-tert-butylphenyl, 4-decylphenyl, 3-ethoxyphenyl, 4-isopropoxyphenyl, 4-(n-nonyloxy)phenyl, 4-(n-octyloxy)phenyl, 4-(n-decyloxy)phenyl, 2,4-dimethoxyphenyl, 4-(t-butoxy)phenyl, 2-methylthiophenyl, 4-(n-nonylthio)phenyl, 4-(n-octylthio)phenyl, mesityl and the like.

Representative R groups when R is heteroaryl are 2-pyrryl, 3-pyrryl, 2-furyl, 3-furyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-indolyl, 2-benzofuryl, 2-benzimidazolyl, 2-imidazolyl, thiophene-2-yl, and the like.

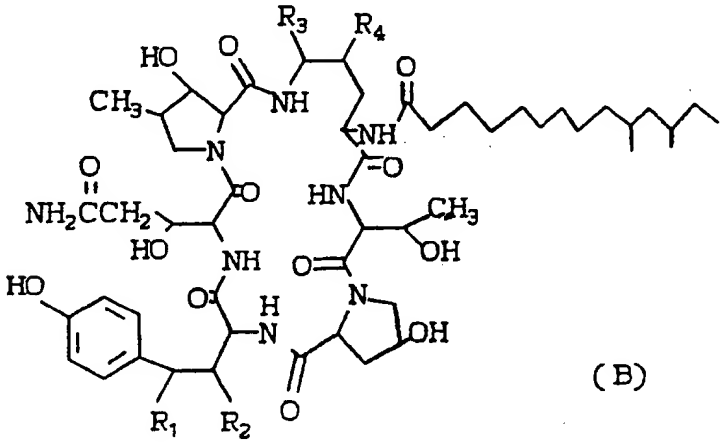
The compounds are prepared by the acylation of a cyclohexapeptide base of formula (A) (hereinafter Compound A).



(A)

The specific base may be referred to as Compound Aa when R_2 is H and R_1, R_3 and R_4 are OH; Compound Ab when R_1, R_2 and R_4 are H and R_3 is OH; and Compound Ac when R_1, R_2, R_3 and R_4 are H.

The compound of formula A is produced by the enzymatic deacylation of an antibiotic of formula (B), hereinafter Compound B.



(B)

The specific antibiotics may be referred to as Compound Ba when R_2 is H and R_1, R_2, and R_4 are OH; Compound Bb when R_1, R_2 and R_4 are H and R_3 is OH; and Compound Bc when R_1, R_2, R_3 and R_4 are H.

The preparation of Compound A and Compound B are hereinafter more fully described.

Preparation of cyclohexapeptide base, Compound A

Compound A may be prepared first by producing Compound B by the cultivation of Zalerion arboricola ATCC 20868, isolating Compound B and thereafter subjecting Compound B to enzymatic deacylation by cultivating Compound B with Pseudomonas acidovorans or Pseudomonas diminuta, or one of the Actinoplanaceae organisms.

In producing Compound B, from Zalerion arboricola ATCC 20868, a frozen culture thereof is inoculated into 54 milliliters of seed medium of the following composition: corn steep liquor, 5.0 g; tomato paste 40.0 g; oat flour 10.0 g; glucose 10.0 g; trace element mixture, 10.0 ml; all in 1000 milliliters of distilled water at pH 6.8. The trace element mixture contains per liter: $FeSO_4 \cdot 7H_2O$, 1 g; $MnSO_4 \cdot 4H_2O$, 1 g; $CuCl_2 \cdot 2H_2O$, 25 mg; $CaCl_2$, 100 mg; H_3BO_3, 56 mg; $(NH_4)_6 Mo_7O_{24} \cdot 4H_2O$, 19 mg; and $ZnSO_4 \cdot 7H_2O$, 200 mg.

The seed flasks are incubated from 3 to 6 days at 25°C with agitation. About 2 ml of resulting culture growth is inoculated into a production medium and incubated at 24° to 28°C for 3 to 30 days with or without agitation. The production medium may be

liquid or solid. Representative of one preferred liquid production medium is of the following composition per liter: D-mannitol, 44 grams; KH_2PO_4, 2 grams; glycine, 2 grams; peptonized milk, 15 grams; lactic acid, 2 grams; trace element mixture (composition same as above), 10 ml; soybean oil, 10 g (pre-sterilization pH of 7.0). Representative of one preferred solid production medium is of the following composition per 250 ml flask: millet, 15 g and base liquid 15 ml. The base liquid is of the following composition per liter: ardamine PH (yeast autolysate, Yeast Products Inc., Clifton, NJ) 33.0 g; sodium tartrate, 6.6 g; $FeSO_4 \cdot 7H_2O$, 0.66 g; monosodium glutamate, 6.6µg; and corn oil, 6.6 ml.

The foregoing media and other media for the production of Compound B are described in copending application Serial No. 374,416, corresponding to EP-A-0405997.

Compound B is then isolated from the fermentation mixture by extracting from the production medium with alcohol, preferably methanol, then partitioning the desired compound into a water-immiscible oxygenated organic solvent such as ethyl acetate, vaporizing the solvent and purifying the residue or concentrate by one or more chromatographic separations as more fully described in said Serial No. 374,416, corresponding to EP-A-0405997.

Compound A may then be produced by subjecting Compound B, obtained as above described, to the action of a deacylating enzyme first produced by inoculating a loopful of Pseudomonas acidovorans ATCC 53942 into 50 milliliters of Luria Bertani medium of the following composition per liter:

Bacto-Tryptone, 10 g; Bacto-Yeast Extract, 5 g and sodium chloride 10 g and solidified with 2 percent agar and incubating for 24 hours with shaking to obtain a seed culture. Cells for deacylation are then grown by diluting a 50 milliliter portion of seed culture 1:500 into fresh Luria-Bertani medium and incubating at 25°C with shaking for 16 hours. Cells are harvested by centrifugation, washed by resuspending in 1 percent sodium chloride, centrifuged and then resuspended in potassium phosphate buffer at pH 6.5.

A solution of Compound B in dimethyl sulfoxide is then added to a stirred suspension of P. acidovorans cells and the mixture maintained for 18 hours to obtain Compound A which is recovered in the supernatant by centrifugation.

Compound A may be isolated by adsorbing the supernatant on HP-20 resin with water, eluting with methanol and concentrating the eluates as more fully described in the aforementioned concurrently filed copending application Serial No. 494,660 (Attorney Docket No 17997).

The preparation of Compound A is carried out by subjecting Compound B in a nutrient medium or in a buffer solution to a deacylating enzyme obtained from or present in intact cells of a microorganism of the family Actinoplanaceae or Pseudomondaceae, generally at a temperature in the range of 20° to 40°C, preferably 25° to 30°C at a pH between about 5.0 and 8.0, with agitation and aeration, for from 16 to 48 hours if an Pseudomondacea is used or from 40 to 60 hours if an Actinoplanaceae is used until the deacylation is judged to be complete as indicated by

the disappearance of the anti-Candida activity of the substrate or as determined by analytical HPLC assay from a previously determined standard. Compound A and its preparation are more fully described and claimed in concurrently filed copending application Serial No. 494,660 (Attorney Docket No. 17997), the teachings of which are incorporated by reference.

Compound B may be prepared by the cultivation of Zalerion arboricola ATCC 20868 in a nutrient medium providing sources of carbon, nitrogen and inorganic salts, preferably in a medium containing a sugar alcohol, for 7 to 14 days with or without agitation, then recovering the desired metabolite by adding methanol and preferably partitioning into an oxygenated solvent such as ethyl acetate, thereafter removing the solvent and dissolving the residue in a solvent suitable for one or more chromatographic separations as more fully described and also described in copending application Serial No. 374,416, and copending application Serial No. 495,019, corresponding to EP-A-0405997, and Serial No. 492,026 (Attorney Docket No. 18082), the teachings of which are also incorporated by reference.

The preparation of Compound I from the cyclohexapeptide (Compound A) may be carried out by intimately contacting Compound A with an active ester

in a solvent. In the formula, R is as previously defined and X is any appropriate leaving group such as chloride, fluoride, bromide, cyanide,

1-benzotriazolate, pentachlorophenoxide, trichlorophenoxide, pivaloate, alkylsulfonate or arylsulfonate.

Suitable solvents include water, dioxane, dimethylformamide, dichloromethane, chloroform, 1,2-dichloroethane and various ethers.

In carrying out the reaction, Compound A, either as a purified compound or as a partially purified sample from the deacylation of the antibiotic (Compound B), is dissolved in dry dimethylformamide and the resulting solution intimately contacted with R-COX. The order of addition is not critical. The resulting mixture is stirred at room temperature for about 16 to 20 hours (conveniently overnight) whereupon a reaction takes place with the formation of Compound I. At the end of this period, the dimethylformamide is removed by concentration in vacuo at 40°C and the resulting residue triturated, preferably sequentially, twice with ether, twice with methylene chloride and finally with ether and then filtered. The filter cake product is generally a free flowing solid and is purified by reverse phase HPLC, typically in 0.5 gram aliquots employing acetonitrile/water as eluting agent. Fractions containing the purified product as determined by C. albicans assay or by U.V. or by refractive index are combined and concentrated first under reduced pressure and then by lyophilization. Candida albicans assay is useful inasmuch as the non-acylated cyclohexapeptide compound is inactive against Candida albicans. Ultraviolet spectrum or refractive index may be employed if the original antibiotic is available as a reference standard.

The compounds of the present invention are antifungal agents and especially useful as antimycotic agents for the control of organisms infecting mammals. Thus, they are useful for the control of such fungal species as Candida albicans, Candida parapsilosis, and other Candida species. They are also useful for the control of Pneumocystis carinii infections in mammals. The compounds are also effective against filamentous fungi including Aspergillus species, Penicillium species, Fusarium species and the like .

In addition to the use of the compounds as therapeutic agents in the treatment of mycotic infections and infections in mammals they may be used wherever growth of fungi is desired to be controlled, e.g. consumer goods, plants and plant parts, plant products, wood and lumber, pulp and paper, and the like. .

When employed for controlling mycotic infections, a therapeutically effective amount is administered but the actual dosage may be varied according to the particular compound employed, the physical condition of the subject being treated, and the severity and nature of the infection. Therapy is usually started at a low dosage and increased to achieve the desired effect.

The compounds may be administered parenterally, orally, topically, by inhalation, by insufflation or by other means for drug administration.

The outstanding properties are most effectively utilized when the compound is formulated into novel pharmaceutical compositions with a

pharmaceutically acceptable carrier according to conventional pharmaceutical compounding techniques.

The novel compositions contain at least a therapeutic amount by weight of the active compound. Generally, it contains at least 1 percent by weight. In preparing the compositions, Compound I is intimately admixed with any of the usual pharmaceutical media.

The compositions may be prepared in oral dosage form. For liquid preparations, the antifungal agent is formulated with liquid carriers such as water, glycols, oils, alcohols, and the like, and for solid preparations such as capsules and tablets, solid carriers such as starches, sugars, kaolin, ethyl cellulose, calcium and sodium carbonate, calcium phosphate, kaolin, talc, lactose, generally with lubricant such as calcium stearate, together with binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage form. It is especially advantageous to formulate the compositions in unit dosage form for ease of administration and uniformity of dosage.

The antifungal agent may be formulated in compositions for injection and may be presented in unit dosage form in ampoules or in multidose containers, if necessary with an added preservative. The compositions may also take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles such as 0.85 percent sodium chloride or 5 percent dextrose in water, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Buffering agents as well

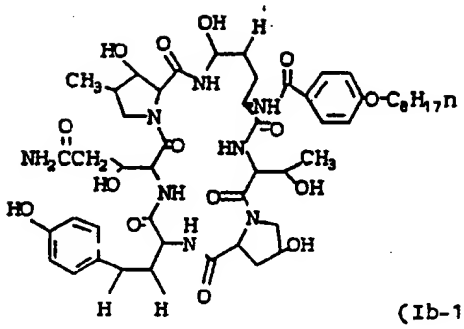
as additives such as saline or glucose may be added to make the solutions isotonic. Alternatively, the active ingredients may be in powder form for reconstituting with a suitable vehicle prior to administration.

The term "unit dosage form" refer to physically discrete units, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the pharmaceutical carrier. Examples of such unit dosage forms are tablets, capsules, pills, powder packets, wafers, measured units in ampoules or in multidose containers and the like. A unit dosage of the present invention will generally contain from 100-200 milligrams of the drugs.

If the application is to be topical, the drug may be formulated in conventional creams and ointments such as white petrolatum, anhydrous lanolin, cetyl alcohol, cold cream, glyceryl monostearate, rose water and the like. Usually a 1 to 2 percent cream or solution is prepared and applied to the area to be treated.

The following examples illustrate the invention but are not to be construed as limiting:

EXAMPLE I



(Ib-1; R=4octyloxyphenyl)

A. Preparation of pentafluorophenyl octyloxybenzoate

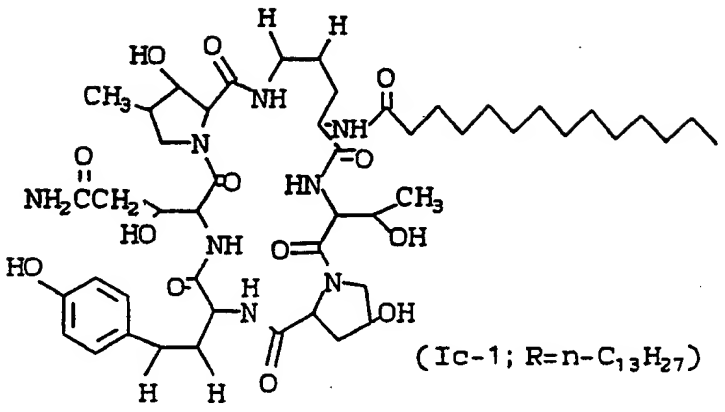
To a suspension of 7.50 grams (30.0 mmol) of octyloxybenzoic acid in 50 milliliters of ethyl acetate was added 6.07 grams (33.0 mmol) of pentafluorophenol. The resulting mixture was cooled in an ice bath and to the cooled solution was added with stirring, 6.46 grams (33.0 mmol) of dicyclohexylcarbodiimide. The mixture was stirred at room temperature for four hours whereupon a reaction took place with the formation of pentafluorophenyl 4-(n-octyloxy)benzoate and dicyclohexylurea. The latter, which precipitated in the reaction mixture, was removed by filtration, the filter cake washed with ethyl acetate, and the filtrate and ethyl acetate wash combined, partitioned with water and the organic solution dried over sodium sulfate. The dried solution was subjected to reduced pressure to remove the solvent and to obtain 11.80 grams (94 percent yield) of the pentafluorophenyl 4-(n-octyloxy)-

benzoate as a white crystalline solid, m.p. 46-47°C.

B. Preparation of Compound Ib-1(R=4-octyloxyphenyl)

5.0 grams of semipurified cyclohexapeptide base, Compound Ab (R_1=R_2=R_4=H;R_3=OH), obtained by deacylation of antibiotic Compound Bd, (R_1=R_2=R_4=H; R_3=OH) in a manner hereinafter described is dissolved in 60 milliliters of dimethylformamide. A 15 milliliter aliquot is added to 0.948 gram of the pentafluorophenyl ester prepared as described in Part A and the mixture allowed to stir overnight (about 16 hours) at room temperature. At the end of this period, the dimethylformamide is removed by concentrating the mixture under reduced pressure at 40°C to obtain Compound Ib-1 as residue. The residue is triturated twice with ether, twice with methylene chloride, again with ether and thereafter purified by preparative HPLC over a "Zorbax" (DuPont) C8 1-inch diameter column in 0.5 gram aliquots and eluting with acetonitrile/water. Eluate fractions containing active ingredient as determined by C. albicans assay are combined and concentrated, first under reduced pressure and then by lyophilization to obtain Compound Ib-1 as a solid.

EXAMPLE II



(Ic-1; R=n-$C_{13}H_{27}$)

A. Preparation of Pentafluorophenyl myristate

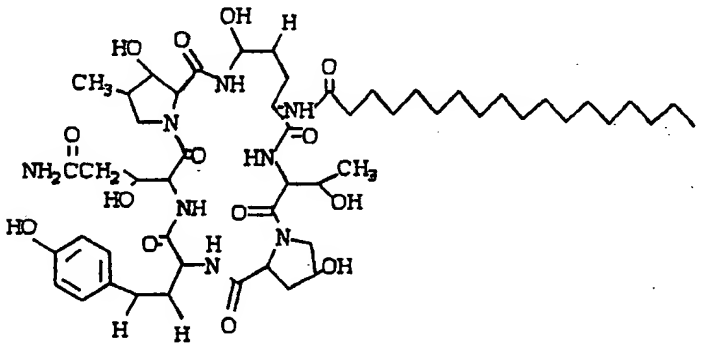
In an operation carried out in a manner similar to that described in Example I, a pentafluorophenyl myristate is obtained by the reaction of 0.519 gram (2.27 mmol) of myristic acid, 0.515 gram of dicyclohexylcarbodiimide and 0.460 gram of pentafluorophenol in 4 milliliters of ethyl acetate. The ester is a light colored solid.

B. Preparation of Compound Ic-1 (R=n-$C_{13}H_{27}$)

In an operation carried out in a manner similar to that described in Example I, a 15 milliliter aliquot of the solution of semipurified Compound Ac (where R_1, R_2, R_3, and R_4 are H) in dimethylformamide prepared in a manner similar to

that described in Example I, is added to the pentafluorophenyl myristate prepared in Part A and the mixture stirred overnight at room temperature. Compound Ic-1 (R=n-$C_{13}H_{27}$) is formed in the reaction mixture and is recovered by removing the dimethylformamide by vaporization under reduced pressure, working up the residue and purifying by preparative HPLC over a "Zorbax" column and thereafter recovering by concentrating and lyophilizing the eluates to obtain a solid in a manner similar to that described in Example I.

EXAMPLE III



(Ib-1; R=n-$C_{17}H_{35}$)

A. Preparation of Pentafluorophenyl stearate

In an operation carried out in a manner similar to that previously described, pentafluorophenyl stearate is obtained by the reaction of 0.647 gram (2.27 mmol) of stearic acid and equivalent

amounts of dicyclohexylcarbodiimide and pentafluorophenol. After working up the reaction mixture, pentafluorophenyl stearate is recovered as a light colored residue.

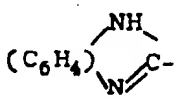
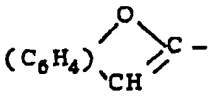
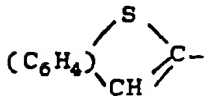
B. Preparation of Compound Ib1 (R=n-$C_{17}H_{35}$)

In a manner similar to that described in Examples I and II, a 15 milliliter aliquot of the solution of semipurified base Compound Ab1 where (R_1, R_2, and R_4 are H and R_3 is OH) in dimethylformamide prepared in the manner described in Example I is added to pentafluorophenyl stearate prepared in Part A and the mixture stirred overnight at room temperature to form Compound Ib-1 in the reaction mixture. The latter is recovered from the reaction mixture by vaporizing off the dimethylformamide under reduced pressure, triturating with ether and methylene chloride, purifying by preparative HPLC and recovering from the eluates by concentration and lyophilization.

EXAMPLE IV

In reactions carried out in a manner similar to those described in the preceding examples, the following compounds are prepared wherein R_1, R_2, R_3 and R_4 are H and R is as designated:

TABLE 1

R	M.W.
n-$C_{10}H_{21}$ -	944
i-C_5H_{11} -	874
t-C_4H_9 -	860
4-(n-$C_8H_{17}O$)C_6H_4 -	1008
4-(n-$C_9H_{19}O$)C_6H_4 -	1022
4-(n-$C_{10}H_{21}O$)C_6H_4 -	1036
4-(n-C_8H_{17})C_6H_4 -	992
4-(n-C_9H_{19})C_6H_4 -	1006
4-(n-$C_8H_{17}S$)C_6H_4 -	1024
4-(n-$C_{10}H_{21}S$)C_6H_4 -	1052
2-C_4H_9NH -	875
2-C_4H_9S -	892
2-C_4H_9O -	876
	920
	920
	936

EXAMPLE V

In reactions carried out in a manner similar to those described in the previous examples, Compounds Ia wherein R_2 is H and R_1, R_3 and R_4 are OH and R is as designated below are prepared.

Table 2

R	M.W.
$n\text{-}C_{10}H_{21}$ -	992
$n\text{-}C_{13}H_{27}$ -	1034
$n\text{-}C_{15}H_{31}$ -	1062
$n\text{-}C_{17}H_{35}$ -	1090
$i\text{-}C_5H_{11}$ -	922
$t\text{-}C_4H_9$ -	908
$4\text{-}(n\text{-}C_9H_{19}O)C_6H_4$ -	1070
$4\text{-}(n\text{-}C_{10}H_{21}O)C_6H_4$ -	1084
$4\text{-}(n\text{-}C_9H_{19})C_6H_4$ -	1054
$4\text{-}(n\text{-}C_8H_{17}S)C_6H_4$ -	1072
$CH_3(CH_2)_5CH{=}CH(CH_2)_9$-	1088
$4\text{-}(n\text{-}C_{10}H_{21}S)C_6H_4$ -	1100
$2\text{-}C_4H_4N$ -	923
$2\text{-}C_4H_3S$ -	940
$2\text{-}C_4H_3O$ -	924
2-benzimidazolyl -	968
2-benzofuranyl -	968
2-benzothienyl -	984

EXAMPLE VI

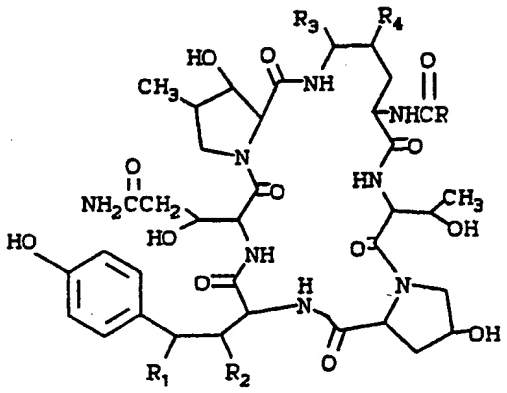
In reactions carried out in a manner similar to those described in the previous examples, Compound Ib wherein $R_1 = R_2 = R_4 = H$ and $R_3 = OH$ and R is as designated below are prepared.

Table 3

R	M.W.
n-$C_{10}H_{21}$ -	960
n-$C_{13}H_{27}$ -	1002
n-$C_{15}H_{31}$ -	1030
i-C_5H_{11} -	890
t-C_4H_9 -	876
4-(n-$C_8H_{17}O$)C_6H_4 -	1024
4-(n-$C_9H_{19}O$)C_6H_4 -	1038
4-(n-$C_{10}H_{21}O$)C_6H_4 -	1052
4-(n-C_9H_{19})C_6H_4 -	1022
4-(n-$C_8H_{17}S$)C_6H_4 -	1040
4-(n-$C_{10}H_{21}S$)C_6H_4 -	1068
2-C_4H_9NH -	891
2-C_4H_9S -	908
2-C_4H_9O -	892
2-benzimidazolyl -	936
2-benzofuranyl -	936
2-benzothienyl -	952
$CH_3(CH_2)_5CH=CH(CH_2)_7$-	1028

WHAT IS CLAIMED IS:

1. A compound having the formula



wherein R is

(a) a straight or branched chain alkyl from 5 to 23 carbon atoms;

(b) a straight or branched chain alkenyl from 5 to 23 carbon atoms;

(c) aryl, preferably, phenyl and substituted phenyl wherein the substituent is C_1 to C_{10} alkyl, C_1 to C_{10} alkoxy or C_1 to C_{10} thioalkoxy; or

(d) heteroaryl selected from the group consisting of pyrryl, thiophenyl, furyl, indolyl, benzothiophenyl, benzofuryl, imidazolyl, benzimidazolyl, and pyridinyl, and

R_1, R_2, R_3 and R_4 are hydrogen or hydroxy to provided a nucleus selected from those in which (1) R_2 is hydrogen and R_1, R_3 and R_4 are hydroxy, (2) R_1, R_2 and R_4 are hydrogen and R_3 is hydroxy and (3) R_1, R_2, R_3 and R_4 are hydrogen.

2. An antibiotic composition which comprises a compound of Claim 1 in admixture with a biologically inert carrier.

3. An antifungal composition which comprises a composition of Claim 2 in which the carrier is a pharmaceutically acceptable carrier.

4. A method for inhibiting fungal growth in consumer goods, plants and plant parts, plant products, wood and lumber, pulp and paper, and the like, comprising applying to the area where growth is to be controlled an antifungally effective amount of the compound of Claim 1.

5. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for treating fungal infections.

6. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for controlling Pneumocystis carinii infections in mammals.

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